REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Objections to the Specification and Claims

As requested by the Examiner, the Specification has been amended to reflect that application Serial No. 09/370,102 has issued as U.S. Patent No. 6,265,547. In addition, claim 10 has been placed into independent form. Withdrawal of the objections to the Specification and claims is therefore to be in order.

Non-consideration of the Information Disclosure Statement is improper

Initially, it is noted that the Examiner failed to completely examine Applicants' invention. Specifically, Applicants object to the Examiner's failure to obtain and fully consider all of the references cited in the parent application and listed on the Form 1449. According to M.P.E.P. § 609:

> ...the examiner ***will consider*** information which has been considered by the Office in a parent application when examining (A) a continuation application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, (B) a divisional application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, or (C) a continuation-in-part application (see MPEP Section 201.06(b)) filed under 37 CFR 1.53(b), and a list of the information need not be submitted in the continuation, divisional, or continuation-in-part application unless applicant desires the information to be printed on the patent. (Emphasis added)

As can be seen from the above, it is mandatory for the Examiner to consider information previously considered in a parent application. The Patent Office has facilities for obtaining copies of the cited information and it is urged that the Examiner make use of these facilities. It is not reasonable, or required by Patent Office policy, for Applicants to provide additional copies of documents already considered in a parent application, especially in view of the vast number of pending applications that Applicants' Assignee, *Incyte Genomics, Inc.*, has at the Patent Office. Refusal by the Examiner to

obtain and consider the documents cited in the parent application clearly is not consistent with Patent Office procedures.

Comments regarding restriction requirement

Claims 29, 32, 34, 43 and 44 are "method of use" claims which depend from product claim 10. Therefore, upon allowance of claim 10, it is believed that claims 29, 32, 34, 43 and 44 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)."

Rejection under 35 U.S.C. §112, second paragraph

Claim 33 is rejected under 35 U.S.C. §112, second paragraph, for alleged indefinitenes. In particular, the Office Action alleges that the claims lacks antecedent basis. Such, however, is not the case.

Claim 33 recites "a ***composition of claim 31***, wherein the antibody is labeled." Claim 31 recites "a composition comprising an antibody of claim 10 and an acceptable excipient." Thus, claim 33 merely further defines the composition by reciting it comprises an antibody that is labeled. The meaning of the claim is clear and, therefore, withdrawal of this rejection is in order.

Enablement rejection under 35 U.S.C. §112, first paragraph

Claims 10, 30, 31, 33 and 35-42 have been rejected as failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph. In particular, the Office Action alleges that the present disclosure does not provide an enabling disclosure of any antibody which specifically binds to any polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1; any antibody which specifically binds to any biologically active fragment of a polypeptide of SEQ ID NO:1; or any antibody which specifically binds to an immunogenic fragment of a polypeptide of SEQ ID NO:1.

Claim 10 has been revised and longer recites antibodies which specifically bind to biologically active or immunogenic fragments of SEQ ID NO:1. This amendment has been made to expedite prosecution of the subject application. Applicants do not concede to the propriety of the Patent Office position relating to enablement of antibodies which specifically bind to fragments of SEQ ID NO:1.

The first paragraph of 35 U.S.C. §112 requires that the Specification describe how to make and use the claimed subject matter. That requirement has been met in the present application. In particular, the Specification describes how to make and use naturally-occurring variants of SEQ ID NO:1.

Independent claim 10, as amended, recites not only that the variant polypeptides are at least 90% identical to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of CJPDC) and SEQ ID NO:2 (the polynucleotide sequence encoding CJPDC), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

> The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature. (Specification at page 10, lines 28-32)
>
> For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at

least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art. (Specification at page 13, lines 25 to page 14, line 8)

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding CJPDZ or closely related molecules may be used to identify nucleic acid sequences which encode CJPDZ. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding CJPDZ, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the CJPDZ encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:2 or from genomic sequences including promoters, enhancers, and introns of the CJPDZ gene.(Specification at page 30, lines 6-16)

See also Example VI at page 38.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the

variant polypeptides of SEQ ID NO:1 recited by the present claims. Methods of producing specifically binding antibodies are described, for example, at pages 22-24 of the Specification.

The Office Action cited Coleman *et al.*, Abaza *et al.*, Lederman *et al.*, and Li *et al.*, as demonstrating that even a single amino acid change can alter protein function. However, these references are not relevant to the case at hand. In these cases, the mutations were "artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by these references would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Thus, the amino acid differences are likely to represent substitutions that do **not** alter protein function. Therefore, the teachings of these references are not relevant to the case at hand, which relates to naturally occurring amino acid sequences.

The Examiner further cites Ngo *et al.* and alleges that due to the fact that the relationships between the sequence of a protein/peptide and its tertiary structure (i.e., its activity) are not well understood and are not predictable, it would require an undue experimentation for one skilled in the art to arrive at polypeptides comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1. However, the document cited by the Examiner relating to structure-antigenicity relationships in proteins is simply not germane to whether one can make and use the polypeptide variants recited by the present claims. That is, regardless of the precise functional characteristics of the SEQ ID NO:1 variants, one can still make those polypeptide variants using the disclosure provided by the present Specification. The polypeptides could then be used in, for example, diagnostic testing, drug discovery, expression profiling, etc.

Furthermore, the Examiner's attention is also directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078) (Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues.

(Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

Claim 10 recites, *inter alia*, "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as CJPDZ-like proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "90% variants" recited by the present claims have a variation that is far less than that of all potential CJPDZ-like proteins related to SEQ ID NO:1, i.e., those CJPDZ-like proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1. Therefore, one would expect the SEQ ID NO:1 variants recited by the present claims to have the functional activities of a CJPDZ-like protein.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement***. [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited variants of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the variants of SEQ ID NO:1.

For at least the above reasons, withdrawal of this rejection is requested.

Written description rejection under 35 U.S.C. §112, first paragraph

Claims 10, 30, 31, 33 and 35-42 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing the subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, had possession of the claimed invention. In particular, the Office Action has alleged that the Specification does not provide an adequate written description of antibodies which specifically bind "90% variants" of SEQ ID NO:1, or antibodies which specifically bind biologically active or immunogenic fragments of SEQ ID NO:1.

Claim 10 has been revised and longer recites antibodies which specifically bind to biologically active or immunogenic fragments of SEQ ID NO:1. This amendment has been made to expedite prosecution of the subject application. Applicants do not concede to the propriety of the Patent Office position relating to written description of antibodies which specifically bind to fragments of SEQ ID NO:1.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46] (Footnotes are omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Examiner concedes that Applicant is possession of an antibody which specifically binds to a polypeptide of SEQ ID NO:1. However, he alleges that Applicant is not in possession of any antibody which specifically binds to any polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.

The subject matter encompassed by Claims 10, 30, 31, 33 and 35-42 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 10 recites a "naturally-occurring polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." The amino acid sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, the Sequence Listing. Variants of SEQ ID NO:1 are described in the specification at, for example, page 3, lines 10-16; page 5, lines 16-19; page 6, lines 9-10; and page 12, lines 24-27.

One of ordinary skill in the art would recognize polypeptide sequences which are variants having a polypeptide sequence at least 90% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited polypeptide variants of SEQ ID NO:1. Moreover, the Specification describes antibodies which specifically bind the SEQ ID NO:1 polypeptides. See, e.g., page 4, lines 8-10; and pages 23-24.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and to antibodies which specifically bind the proteins) commonly

emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides to which the claimed antibody specifically binds in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 10 recites chemical structure to define the claimed genus:

> 10. (Once Amended) An isolated antibody which specifically binds to an isolated polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant

evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to antibodies which specifically bind cell junction PDZ related proteins, including cell junction PDZ proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as cell junction PDZ proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites antibodies which specifically bind a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 233 amino acid residues). This variation is far less than that of all potential cell junction PDZ proteins related to SEQ ID NO:1, i.e., those cell junction PDZ proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of September 11, 1998. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the

applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies that bind specifically to "variants" of SEQ ID NO:1 at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner *et al.* Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be withdrawn.

Rejection under 35 U.S.C. §103(a)

Claims 10, 31, 33 and 35-42 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent, No. 6,051,374 in view of U.S. Patent No. 6,210,675. In addition, §103 rejections of claim 10 and 30 were applied over the '374 and '675 patents further in view of either Owens et al

(J. Immunol. Methods, 168 (2): 149-165, 1994) or Bird et al. (Science, 242 (4877): 423-426, 1988). These rejections are traversed.

At the outset, the Office Action has acknowledged that antibodies which specifically bind the full length SEQ ID NO:1 polypeptides are patentable over the prior art. See paragraph 15 on page 8 of the Office Action. However, the Office Action has asserted that the '374 patent discloses a certain immunogenic fragment of SEQ ID NO:1 and that it would have been obvious to produce antibodies to this fragment in view of the '675 patent.

While not conceding the propriety of the Patent Office position, claim 10 has been revised to delete recitation of antibodies which specifically bind to immunogenic fragments of SEQ ID NO:1 in order to expedite prosecution of the subject patent application. None of the applied art suggests antibodies as defined by the amended claims. Therefore, withdrawal of the §103 rejections is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: 20 September 2002

Richard C. Ekstrom
Reg. No. 37,027
Direct Dial Telephone: (650) 843-7352

Date: September 20, 2002

Sreenivasarao Vepachedu
Reg. No. 46,395
Direct Dial Telephone: (650) 845-5735

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at line 1 of page 1 has been amended as follows:

This application is a divisional application of U.S. application Serial Number 09/370,102 filed on August 6, 1999, now U.S. Patent Number 6,265,547, which is a divisional application of U.S. application Serial Number 09/151,611 filed on September 11, 1998, [issued on Septmeber 28, 1999, as] now U.S. Patent Number 5,958,731, entitled CELL JUNCTION PDZ PROTEIN, the contents all of which are hereby incorporated by reference.

IN THE CLAIMS:

Claims 1, 2 and 9 have been canceled.

Claims 10 and 45 have been amended as follows:

10. (Once Amended) An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.

45. (Once Amended) An isolated antibody of claim 10 which specifically binds to a polypeptide [of claim 2] comprising the amino acid sequence of SEQ ID NO:1.

Claim 46 has been added as follows:

46. (New) An isolated antibody of claim 10 which specifically binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.